25995A-FWC

PATENT

#13
3-13-86

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Arne Elof Brandstrom

Serial No. : 640,020 Examiner : J. Fan

Filed : August 10, 1984 Group Art No. 121

For : NOVEL COMPOUNDS

February 27, 1986

R E S P O N S E

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on

February 27, 1986 .

Marina T. Larson — Attorney's Name
P-32,038 — Reg. No.

Marina T. Larson — Attorney's Signature
February 27, 1986 — Date of Signature

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R :

This is in response to the Official Action dated August 29, 1985 for the above-captioned application. Applicant requests a three-month extension of time to respond to the Official Action and encloses the required fee. Reconsideration of the application in view of the remarks hereinbelow is respectfully requested.

Claims 1-4 and 16-31 are pending in this application. These claims encompass the base addition salts of omeprazole, pharmaceutical base addition salts of omeprazole, pharmaceutical preparations containing these salts, and a method of treating gastric disorders using these salts. The base addition salts provide surprisingly improved stability relative to neutral omeprazole, and are therefore substantially superior where storage and subsequent distribution are contemplated.

In the outstanding Official Action, the Examiner maintained her rejection of claims 1-4 and 16-31 under 35 U.S.C. § 103 as obvious over Senn-Bilfinger, European Patent Applications Nos. 5,129 and 45,200 and Elderfield, all taken together. EPA 5,129 and EPA 45,200 disclose omeprazole in its neutral form. Elderfield discloses that the -NH- group of unsubstituted benzimidazole can act as either a base or an acid. Senn-Bilfinger discloses a compound which is allegedly structurally similar to Omeprazole, having a $-CF_3$ substituent rather than $-OCH_3$, and base addition salts thereof.

In response to the previous Official Action, applicant submitted Declarations under Rule 132 showing the superior stability of base addition salts of omeprazole as compared with neutral omeprazole. In the outstanding Official Action, the Examiner acknowledges receipt of these declarations, but states that they are unpersuasive for three reasons.

The Examiner's first reason for finding the declarations unpersuasive relates to the scope of the evidence presented. The Examiner alleges that the evidence is not commensurate with the scope of the claims, because only three base addition salts are tested although eight salts are claimed.

Further, the Examiner objects to the fact that data is only presented for degradation at 37°C and 50°C, and not at room temperature.

It is, of course, well established that the evidence of unexpected superiority must be commensurate with the scope of the claims in order to negate a finding of prima facie obviousness. This does not mean, however, that an applicant must present data relating to each and every claimed compound. In re Kollman, 201 U.S.P.Q. 193, 199 (C.C.P.A. 1979). In the present case, one skilled in the art could reasonably conclude that the observed improvements in stability were due to properties of base addition salts of omeprazole, and not due to some special properties of the cation. The evidence presented provides an adequate basis for reasonably concluding that the compositions included in the claims would behave in the same manner as the three test compositions. Thus, the present case can be distinguished from cases such as In re Greenfield, 197 U.S.P.Q. 227 (C.C.P.A. 1978), wherein declarations were found to be insufficient.

Turning to the temperature at which the tests were carried out, applicant notes that it is normal and accepted procedure to conduct drug stability tests under accelerated conditions, i.e., at elevated temperature and/or at high relative humidity. Temperature and humidity are the two parameters which normally have the greatest impact on a drug's stability, but testing under normal storage conditions is considered too time-consuming for routine use. For this reason, stability is tested at elevated temperature, and/or at high humidity so that results can be obtained more promptly.

The Examiner's second reason for finding the declarations unpersuasive is that the samples tested were the chemical compound only, and not in pharmaceutical formulations.

The testing of an active substance by itself, however, is normal and accepted practice within the pharmacceutical industry. Indeed, since the complete pharmaceutical formulation will have been tailored to achieve maximum stability, the only proper way to compare the stability of two compounds is to test them as pure compounds. It is, of course, normal and indeed required to test the ultimate pharmaceutical formulation for stability prior to marketing, but this requirement in no way reflects on the meaningfulness or adequacy of the tests on the compounds per se.

The Examiner's third reason for finding the declarations unpersuasive relates to the data presented in Dr. Pilbrandt's declaration. These data show some admittedly equivocal results at intermediate time periods, and because of this, the Examiner finds the declaration unconvincing.

The results for the intermediate time periods were included in Dr. Pilbrant's declaration in the interest of candor and good faith. The equivocal nature of these results reflects the error which is inherent in the determination of small concentrations of degradation products using high-performance liquid chromatography (HPLC), the technique employed by Dr. Pilbrant.[1] Because of this inherent error, meaningful comparison of the percent degradation at intermediate times is not really

[1]The error in determining low concentrations of degradation products arises due to overlapping peaks in the HPLC chromatogram. The area of each peak is determined, the area being proportional to the concentration of the compound represented by the peak. When the concentration of a degradation compound is low, the peak is small, and the precision with which the peak area can be measured is also low. Moreover, any impurities or other compounds which elute from the HPLC column at the same time as the degradation compound will contribute to the area of the peak, thus making the concentration of the degradation compound appear artificially large. As the concentration of a degradation compound increases, the ability to measure the peak area improves, and the realative impact of any impurities declines.

possible, and only data from the later times, when a significant amount of degradation has occurred in the neutral omeprazole sample, are really meaningful.

From the foregoing remarks, it can be seen that the Examiner's continued rejection of the pending claims is grounded largely in her failure to appreciate the normal and accepted test procedures used within the pharmaceutical industry. Once one is aware that the tests conducted were procedurally adequate, the rejection is reduced to the Examiner's assertion that the testing of three base addition salts of omeprazole does not support the scope of the claims. The Examiner has offered no reasons, however, why one skilled in the art might expect one base addition salt of omeprazole to behave in a manner different from another. The similarities within the claimed group of compounds are substantial, and applicant submits that no reasonable basis exists to conclude that the sodium, magnesium and calcium salts tested are not representative of the salts claimed.

Furthermore, it is clear from the data presented in the declarations that the base additions salts of omeprazole are substantially more stable than neutral omeprazole. As a solid, neutral omeprazole undergoes nearly four times more degradation in six months than the calcium salt, the least stable of the claimed compounds reported in the Pilbrant declaration. In solution, the Brandstrom declaration demonstrates that the half-life of sodium omeprazole is more than 25 times as long as that of neutral omeprazole. These data clearly establish the superior stability of the claimed compounds, and applicant submits that the pending claims are therefore unobvious.

Applicants also note that only pending claims 1, 16, 20, 24 and 28 recite the broad range of cations to which the Examiner objects. Claims 2, 17, 21, 25 and 29 are limited to

sodium, potassium, calcium and magnesium salts. Data for three of these cations is reported in the Pilbrandt declaration. Only for the potassium salt are results not reported. It is, however, well within the reasonable skill in the art to expect similar behavior of potassium and sodium salts. The scope of the declarations is, at a minimum, entirely adequate to support these claims. Thus, applicants submit that even if the Examiner finds the arguments herein regarding the scope of the evidence unconvincing and maintains her rejection, the continued rejection of claims 2, 17, 21, 25 and 29 would be inappropriate.

The remaining claims are of even narrower scope, and are entirely supported by the declarations. Claims 3, 18, 22, 26 and 30 recite only sodium salts of omeprazole. Claims 4, 19, 23, 27 and 31 recite only magnesium salts. These claims are all clearly within the scope of the declarations submitted and should be allowed.

The final point in the Examiner's rejection relates to an argument raised on Page 4 of the amendment of July 5, 1985. In that argument, applicant noted that since the $-CF_3$ group of the Senn-Bilfinger compounds was an electron withdrawing group, it would stabilize any anion formed, and thereby increase the acidity of the Senn-Bilfinger compound. Page 831 of Morrison and Boyd's Organic Chemistry was cited to show that an electron withdrawing group would indeed resonance stabilize such an anion, leading to greater acidity.

The Examiner has alleged that this argument is not well founded, because $-CF_3$ is not specifically listed on Page 831 as an electron withdrawing group. Further, the Examiner has introduced some confusion by asserting as part of her rejection that the $-CF_3$ should stabilize the anion. Since this is precisely the effect that applicant's amendment of July 5, 1985

said the $-CF_3$ group would have, the basis for the rejection is not apparent. Nonetheless, applicant will restate the argument here in the interests of clarity.

The substituted benzimidazoles of Senn-Bilfinger and omeprazole differ by a single substituent group: Senn-Bilfinger having a $-CF_3$ group where omeprazole has an $-OCH_3$ group. The nature of these groups will effect the acidity of the benzimidazole moiety via resonance stabilization or destabilization of the resulting anion. As suggested by Page 831 of Morrison and Boyd's Organic Chemistry electron withdrawing groups will stabilize the anion, thus enhancing acidity, while electron-donating groups destabilize the anion, thus reducing acidity.

The $-OCH_3$ substituent of omeprazole is an electron-donating group, as indicated on Page 831. Thus, omeprazole will be less acidic than the unsubstituted analog. Conversely, $-CF_3$ is an electron withdrawing group, making the Senn-Bilfinger compound more acidic than either the unsubstituted analog or omeprazole. $-CF_3$ is not explicitly listed on Page 831, but based on the pronounced electronegativity of fluorine atoms, one skilled in the art wouuld immediately recognize that a carbon atom with three fluorines attached will be an electron withdrawing group.

For the reasons discussed above, applicant submits that pending claims 1-4 and 16-31 are allowable on the present record. Prompt reconsideration and allowance of the pending claims are respectfully requested.

Respectfully submitted,

Marina T. Larson

Allan H. Bonnell
Patent Office Reg. No. 22,059

Attorney for Applicant

Marina T. Larson
Patent Office Reg. No. P-32,038

Agent for Applicant